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Nature of Intermediates in Organo-SOMO Catalysis of α-Arylation of Aldehydes

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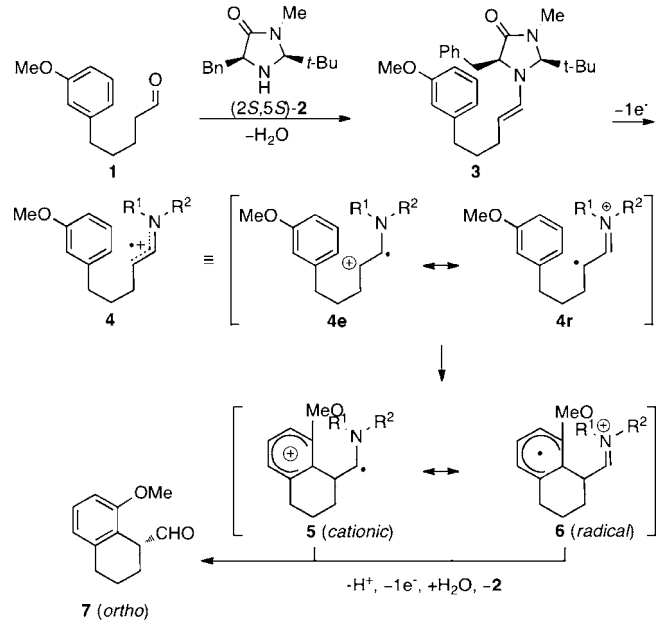
Abstract: The intramolecular α-arylation of aldehydes via organo-SOMO catalysis was investigated using density functional theory (B3LYP and M06-2X functionals). The geometries, spin densities, Mulliken charges, and molecular orbitals of the reacting enamine radical cations were analyzed, and the nature of the resulting cyclized radical cation intermediates was characterized. In agreement with experimental observations, the calculated 1,3-disubstituted aromatic system shows *ortho* selectivity, while the 1,3,4-trisubstituted systems show *para, meta* (instead of *ortho, meta*) selectivity. The selectivity change for the trisubstituted rings is attributed to a distortion of the *ortho* substituents in the *ortho, meta* cyclization transition structures that causes a destabilization of these isomers and therefore results in selectivity for the *para, meta* product.

Introduction

Organo-SOMO catalysis has recently become an important activation mode for asymmetric α-allylation,[1a] α-enolation,[1b] α-vinylation,[1c] α-carbo-oxidation,[1d] α-nitroalkylation,[1e] and intramolecular α-arylation[1f,2] of aldehydes. One of our groups has shown that the reactions proceed via a three-π-electron radical cation species generated by one-electron oxidation of a chiral enamine. In reports on intramolecular α-arylation reactions from the Nicolaou group[1f] and one of our laboratories,[2] the cyclization of enamine radical cation **4** was shown to selectively attack *ortho* to the methoxy group (Scheme 1).[3,4] It was proposed that an intermediate best represented as **5** (rather than **6** described earlier[1f]) was involved. The Nicolaou group showed that 1,3,4-trisubstituted aldehydes **8**−**10**, however, react to give *para* aryl products **11**−**13** (Scheme 2). We have explored the mechanisms of these reactions, particularly the nature of the intermediates and the origins of selectivity, using quantum-mechanical calculations.[5]

Scheme 1



Results and Discussion

Density functional theory (DFT) calculations at the UB3LYP level were performed on the simple model radical cation **14***. Bond distances, spin densities, Mulliken charges, and singly occupied molecular orbital (SOMO) coefficients of **14*** are shown in Figure 1. The C1−C2 bond distance (1.39 Å) is longer than that of an enamine (1.34 Å), and the N−C1 distance (1.33 Å) is closer to that of an iminium ion (1.29 Å) than that of an enamine (1.40 Å). The majority of the spin is on the carbon β

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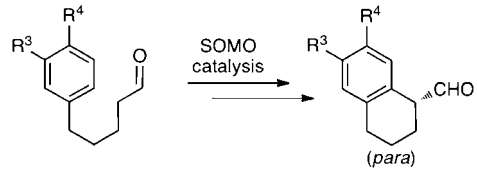
(1) (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (c) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (d) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494. (e) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332. (f) Nicolaou, K. C.; Reingruber, R.; Sarlah, D.; Bräse, S. *J. Am. Chem. Soc.* **2009**, *131*, 2086. Correction: *J. Am. Chem. Soc.* **2009**, *131*, 6640.
(2) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640.
(3) The authors of ref 1f used (2*R*,5*R*)-**2** as the catalyst. Because our calculations and experiments were performed with the opposite enantiomer, this paper reports the study of catalyst (2*S*,5*S*)-**2**.
(4) For *ortho*-selective radical additions to aromatics, see: (a) Tiecco, M.; Testaferri, L. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, p 61. (b) Guadarrama-Morales, O.; Mendéz, F.; Miranda, L. D. *Tetrahedron Lett.* **2007**, *48*, 4515. (c) Muchowski, J. M.; Cho, I. S.; Jaime-Figueroa, S.; Artis, R. D. *J. Org. Chem.* **1994**, *59*, 2456. (d) For a study of the stability of cyclohexadienyl radicals, see: Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 4074.

Scheme 2



8: $R^3 = R^4 = OMe$
9: $R^3 = OMe$; $R^4 = Me$
10: $R^3, R^4 = -OCH_2O-$

11: $R^3 = R^4 = OMe$
12: $R^3 = OMe$; $R^4 = Me$
13: $R^3, R^4 = -OCH_2O-$

to the nitrogen (C2), and the charge is mainly on the iminium carbons α to the nitrogen, as in ammonium cations.[6] A molecular orbital (MO) analysis showed that the largest coefficient of the singly occupied π orbital lies on C2. The species is of course a resonance hybrid (**14**) but is best characterized as an alkyl radical conjugated to an iminium cation. The spin density is consistent with major contributions from **14a** and **14b**.

The enamine radical cation of propanal with catalyst **2** (**15-*E****) is similar (Figure 2). The reported enantioselectivity range with this catalyst was 84−98%.[1f,2] The lowest-energy conformer is expected to directly attack from the less hindered *Si* ("bottom") face of 1**5-*E****, which is in agreement with the experimentally observed stereoisomer.[3] The lowest-energy *Z* isomer **15-*Z****, which would give the opposite enantiomer of the product, is 3.0 kcal/mol higher in energy than **15-*E****.

Having established the charge and spin density distribution of the enamine radical cations, we investigated the transition structures for *para* and *ortho* attack of achiral radical cation **16*** on the anisole ring (Figure 3). In agreement with experimental results, *ortho* attack (**TS1***) is predicted to be favored over *para* attack (**TS2***) by 0.5 kcal/mol. The activation free energy for attack on the unsubstituted benzene is ∼3 kcal/mol higher (18.3 kcal/mol), in agreement with the failed cyclization of this arene under the same reaction conditions.[7]

The endergonicities for formation of **17*** and **18*** suggest that the cyclization step is easily reversible. Since **17*** should accumulate in higher concentrations than **18***, the potential subsequent steps were explored. Deprotonation of the more abundant and more rapidly formed **17*** leads to the favored *ortho* product. Oxidation of **17***, as suggested in ref 2, was calculated to be at least as feasible as oxidation of the enamine that gives **16***.[8] Radical trapping of **17***, followed by deprotonation/aromatization and iminium ion hydrolysis, or trapping of the iminium ion by water,[9] followed by oxidation and subsequent deprotonation/aromatization and hydrolysis, are potential fates of the cyclized radical cations. Both of these

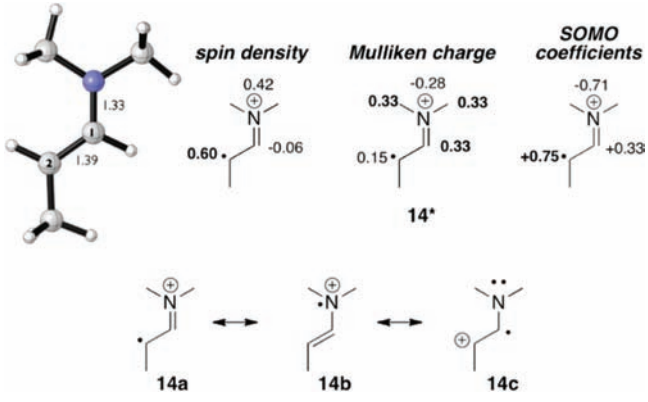


Figure 1. Model enamine radical cation **14*** [UB3LYP/6-31G(d)].

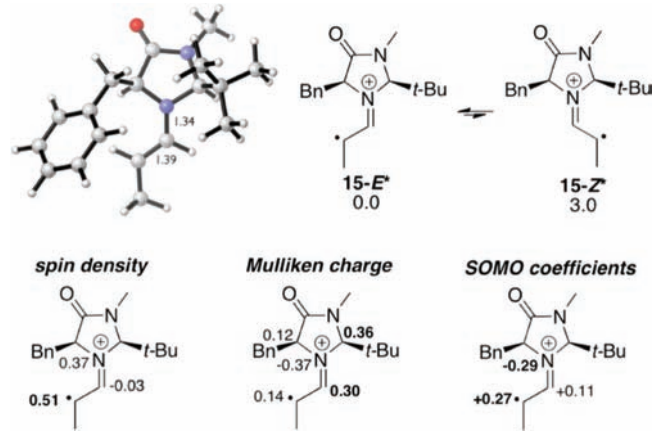


Figure 2. Model enamine radical cation **15*** [UB3LYP/6-31G(d)].

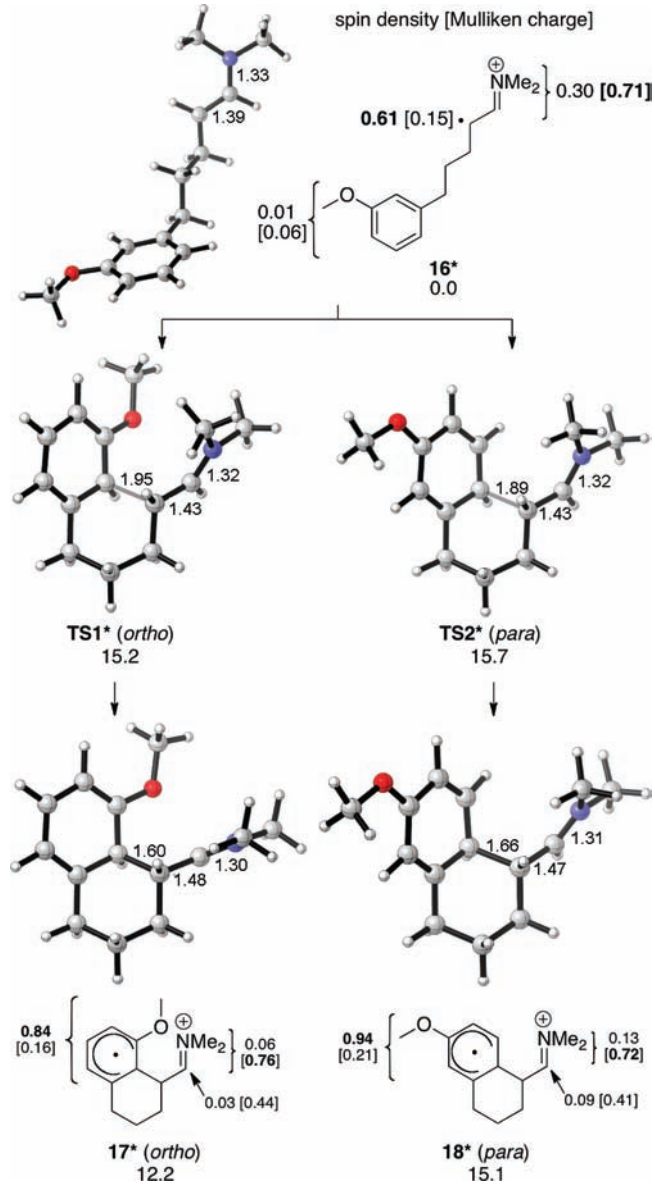


Figure 3. Intramolecular α-arylation of **16*** [UB3LYP/6-31G(d) Δ*G* values for aqueous solution at 268 K; optimizations in CPCM water].

trapping mechanisms are expected to occur readily with little rate dependence on *ortho/para* selectivity, so the greater stabilization of the cyclohexadienyl radical by the methoxy

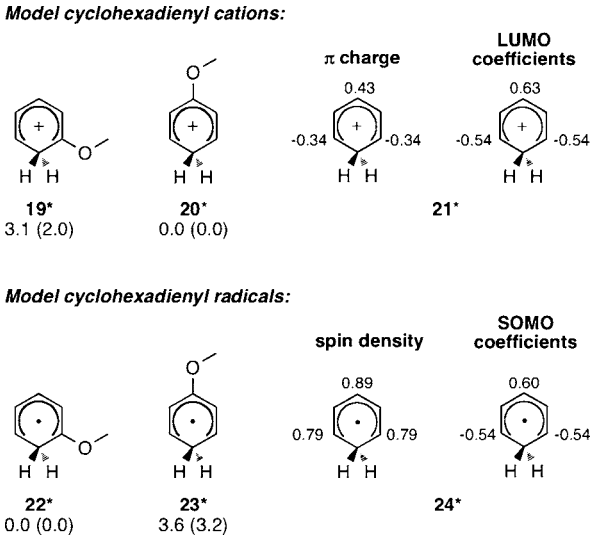


Figure 4. Model *ortho*- and *para*-methoxycyclohexadienyl cations and radicals [CBS-QB3 ΔH values; B3LYP/6-31G(d) values are given in parentheses].

group at the 1-position rather than the 3-position provides the basic origin of the selectivity. Exactly the opposite would happen were the intermediate to have primarily cyclohexadienyl cation character. CBS-QB3 calculations of model 1- and 3-methoxycyclohexadienyl cations (**19*** and **20***, respectively; Figure 4) showed that the 3-methoxy cation (**20***) is 3.1 kcal/mol more stable than the 1-methoxy cation (**19***). This can be explained by the stabilization of the positive charge of **21*** at C3 by the methoxy group and a larger LUMO coefficient at this position. On the contrary, the 1-methoxycyclohexadienyl radical (**22***) is 3.6 kcal/mol more stable than the 3-methoxy radical (**23***). Both the spin density and SOMO coefficient of **24*** are larger at C3 than at C1. Thus, the explanation for the relative stabilities of cyclohexadienyl radicals requires more than a simple spin density or MO analysis.[10]

We next investigated the cyclization of aldehydes **8**−**10** via the model dimethylenamine radical cations (Figures 5−7). Our calculations show that *para*, *meta* cyclization is favored over *ortho*, *meta* cyclization by 2.4−3.4 kcal/mol, in agreement with experiment. The intermediates, **26***−**27***, **29***−**30***, and **32***−**33*** have the same predominantly cyclohexadienyl radical character as described for **17*** and **18***. The *para*, *meta*

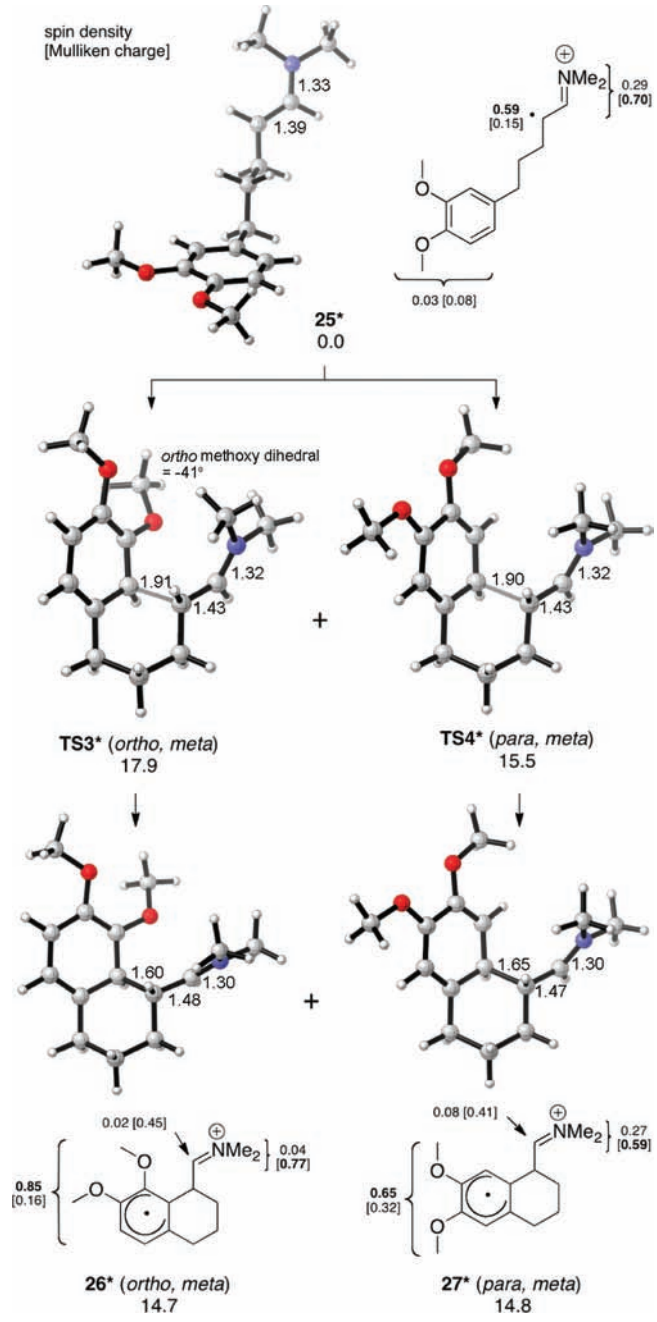


Figure 5. Intramolecular α-arylation of **25*** [UB3LYP/6-31G(d) ΔG values for aqueous solution at 268 K; optimizations in CPCM water].

cyclization barriers **TS4***, **TS6***, and **TS8*** are similar to **TS1*** (15−16 kcal/mol), while the *ortho*, *meta* cyclization barriers **TS3***, **TS5***, and **TS7*** are larger than **TS1*** (∼18 kcal/mol). These results suggest that the *meta* substituent (R^4) causes the *ortho*, *meta* transition states to be destabilized. Since the activation energies of **TS3***, **TS5***, and **TS7*** are similar to that of the unsubstituted system, it is possible that the *ortho*, *meta* cyclizations do not occur under the reaction conditions (−30 °C). The M06-2X functional has been found to be reliable for weak dispersion interactions and has been used successfully for organic reactions involving radicals,[11] so we applied this method by applying single-point calculations to the B3LYP-optimized geometries. The results are summarized with the B3LYP energies in Table 1.

(5) With the exceptions of **14***, **15-*E****, **15-*Z****, and **19***−**24***, which were optimized in the gas phase, all of the geometries were optimized in water (CPCM model) using DFT at the UB3LYP/6-31G(d) level, as implemented in the Gaussian03 suite of programs (Frisch, M. J.; et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004). Model cations and radicals **19***−**24*** were optimized using both CBS-QB3 (Gaussian 03) and UB3LYP/6-31G(d). All of the stationary points were verified by vibrational frequency analysis. Single-point calculations were also performed using M06-2X/6-31+G(d), as implemented in Gaussian09 (Frisch, M. J.; et al. *Gaussian 09*, revision A.1; Gaussian, Inc.: Wallingford, CT, 2009). Each of the computed structures is designated with an asterisk (*). The resulting energies are reported in kcal/mol in all figures and schemes.

(6) (a) Olah, G. A.; Prakash, G. K. S.; Rasul, G. *Chem.—Eur. J.* **2009**, *15*, 8443. (b) No, K.-T.; Grant, J. A.; Jhon, M.-S.; Scheraga, H. A. *J. Phys. Chem.* **1990**, *94*, 4740. (c) Würthwein, E.-U.; Sen, K. D.; Pople, J. A.; Schleyer, P. v. R. *Inorg. Chem.* **1983**, *22*, 496.

(7) Unpublished results.

(8) See the Supporting Information.

(9) For an example of water-assisted reactivity of radical cations, see: Heinemann, C.; Demuth, M. *J. Am. Chem. Soc.* **1999**, *121*, 4894.

(10) This study is underway and will be reported in due course.

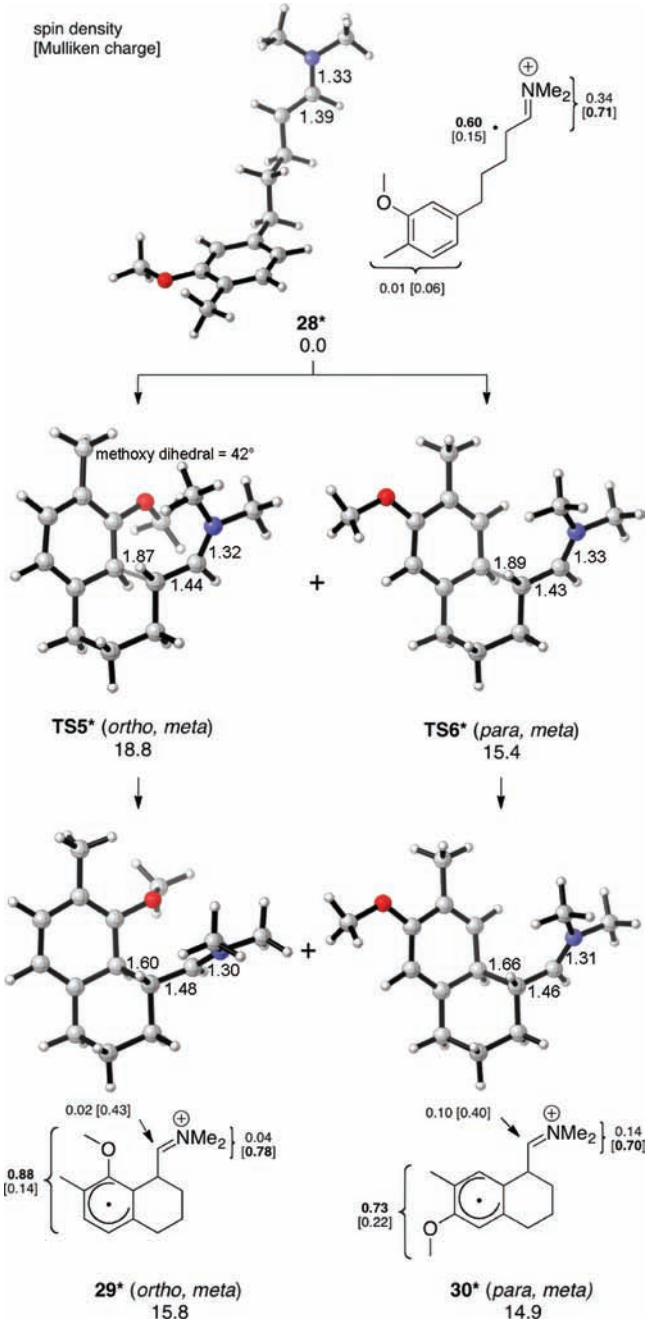


Figure 6. Intramolecular α-arylation of **28*** [UB3LYP/6-31G(d) Δ*G* values for aqueous solution at 268 K; optimizations in CPCM water].

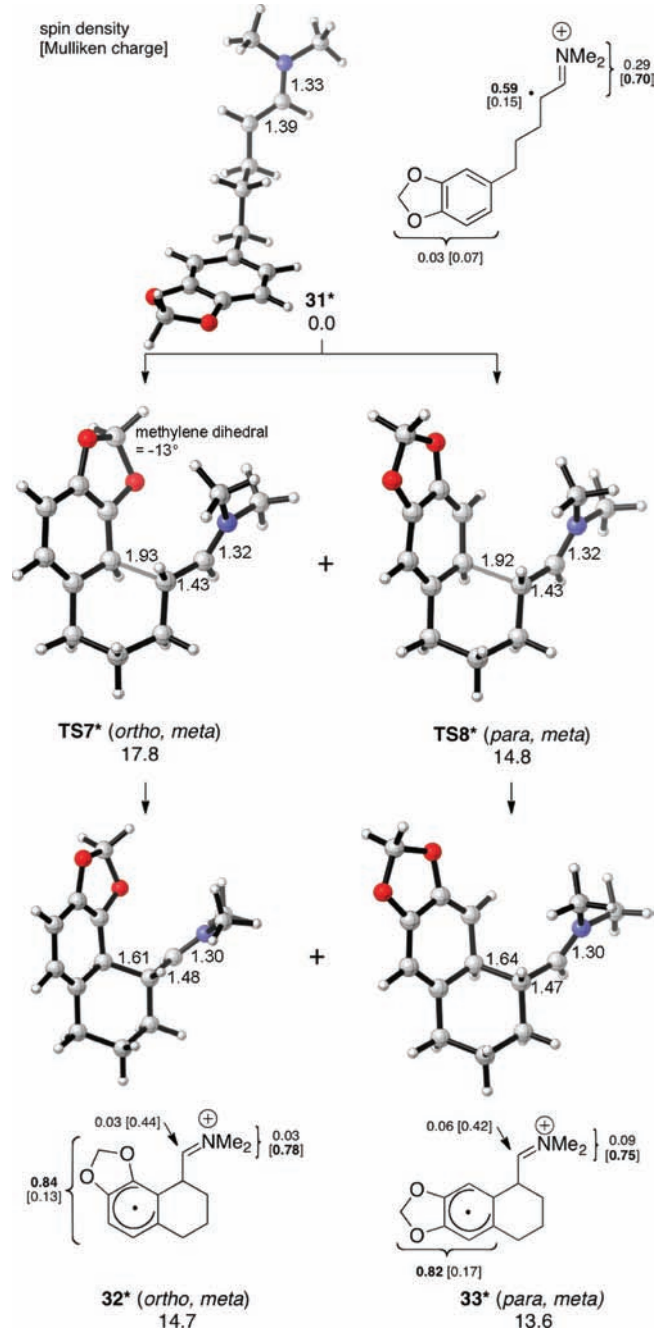
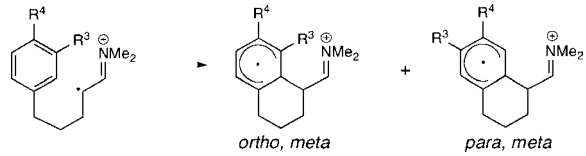


Figure 7. Intramolecular α-arylation of **31*** [UB3LYP/6-31G(d) Δ*G* values for aqueous solution at 268 K; optimizations in CPCM water].

In comparison with the B3LYP activation free energies, the M06-2X barriers are 2.1−4.2 kcal/mol lower. The M06-2X reaction free energies are less endergonic than the B3LYP values by 4.6−6.1 kcal/mol. The calculated M06-2X selectivities are in good agreement with experimental observations and B3LYP predictions. For cyclization of monomethoxy radical cation **16***, the difference between **TS1*** and **TS2*** is 1.5 kcal/mol at the M06-2X level, compared with 0.5 kcal/mol using B3LYP. The *ortho* cyclized radical cation **17*** is 4.4 kcal/mol more stable than the *para* isomer **18*** using M06-2X. Of the 1,3,4-trisubstituted systems, **25*** and **31*** show a 2.3 kcal/mol selectivity for *para*, *meta* cyclization at the M06-2X level (**TS4*** vs **TS3*** and **TS8*** vs **TS7***), while **28*** shows a smaller selectivity of 1.3 kcal/mol (**TS6*** vs **TS5***). M06-2X calculations showed little difference in the relative stabilities of *para*, *meta* cyclized radical cations **27*** and **30*** with respect to the *ortho*, *meta* isomers (**26*** and **29***, respectively). The *para*, *meta* radical cation **33*** is more stable than the *ortho*, *meta* isomer **32*** by 1.0 kcal/mol. In view of the lack of stability difference between the *ortho*, *meta* and *para*, *meta* cyclized radical cations as well as the consistently high *ortho*, *meta* arylation activation barriers, which are within 1.4 kcal/mol of the barrier for the completely unreactive unsubstituted aldehyde, we conclude that the selectivity of 1,3,4-trisubstituted aldehydes **8**−**10** is controlled by the activation free energies.

(11) For examples, see: (a) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2008**, *112*, 1095. (b) Hohenstein, E. G.; Chill, S. T.; Sherrill, C. D. *J. Chem. Theory Comput.* **2008**, *4*, 1996. (c) Valdes, H.; Pluháčková, K.; Pitonák, M.; Řezáč, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2747.

Table 1. Intramolecular α-Arylation of Aryl Rings



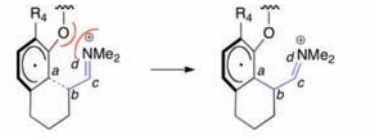
		UB3LYP/6-31G(d)[a]				M06-2X/6-31+G(d)[a,b]			
		$\Delta G^{\ddagger}$		ΔG_{rxn}		$\Delta G^{\ddagger}$		ΔG_{rxn}	
entry	uncyclized radical cation	*ortho, meta*	*para, meta*	*ortho, meta*	*para, meta*	*ortho, meta*	*para, meta*	*ortho, meta*	*para, meta*
1	R^3 = OMe, R^4 = H, **16***	15.2	15.7	12.2	15.1	12.1	13.6	6.1	10.5
		TS1*	**TS2***	**17***	**18***	**TS1***	**TS2***	**17***	**18***
2	R^3 = R^4 = OMe, **25***	17.9	15.5	14.7	14.8	14.7	12.4	9.0	8.9
		TS3*	**TS4***	**26***	**27***	**TS3***	**TS4***	**26***	**27***
3	R^3 = OMe, R^4 = Me, **28***	18.8	15.4	15.8	14.9	14.6	13.3	9.9	10.2
		TS5*	**TS6***	**29***	**30***	**TS5***	**TS6***	**29***	**30***
4	R^3, R^4 = $-OCH_2O-$, **31***	17.8	14.8	14.8	13.6	14.7	12.4	9.2	8.2
		TS7*	**TS8***	**32***	**33***	**TS7***	**TS8***	**32***	**33***
5	R^3 = R^4 = H, **34***	18.3, **TS9***		16.0, **35***		16.0, **TS9***		10.7, **36***	

[a] UB3LYP/6-31G(d) thermal corrections at 268 K were applied. [b] Reported values represent single-point calculations at the UB3LYP/6-31G(d)-optimized geometries.

The destabilization of *ortho*, *meta* transition states **TS3***, **TS5***, and **TS7*** relative to *para*, *meta* isomers **TS4***, **TS6***, and **TS8*** can be explained by the conformation of the *meta* substituent R^3. It has been established that the methoxy groups of anisole prefer a planar conformation.[12] The same conformational preference holds true for *ortho* (**22***) and *para* (**23***) methoxycyclohexadienyl radicals. In *ortho*, *meta* transition states **TS3*** and **TS5***, the *ortho* methoxy group cannot be planar because of steric hindrance from the *meta* R^4 group, raising the energies relative to the *para*, *meta* transition states. The *meta* oxygen of *ortho*, *meta* transition state **TS7*** is also nonplanar because the parent 1,3-benzodioxole prefers a nonplanar conformation in which the methylene moiety is puckered with respect to the five-membered ring.[13] This is due to the anomeric effect, which involves stabilization by n → σ^* interactions between the oxygen lone pairs and the C−O σ^* orbitals of the puckered conformation. Electrostatic repulsion may exist between the oxygen lone pairs and the iminium moiety of the catalyst. This repulsion is relieved in cyclized radical cations **26***, **29***, and **32*** as the iminium group bends away from the cyclohexadienyl radical (see the comparison of the dihedral angles a−b−c−d in Table 2).

In conclusion, the selectivity of the α-arylation reactions is attributed to the activation energies and relative stabilities of the isomeric transition states. In the case of the monomethoxyaryl system **1***, both *ortho* and *para* arylation barriers are possible under the reaction conditions. These reactions are endergonic, and the transition-state energies are related to the relative stabilities of the resulting cyclized radical cation intermediates. For the more highly substituted aldehydes **8***−**10***, R^3 is distorted from planarity, which raises the energy of the *ortho*, *meta* transition states with respect to the *para*, *meta* isomers. The *ortho*, *meta* activation energies are similar to those of unreactive aldehydes. Thus, *ortho*, *meta* cyclization does not occur under the reaction conditions, resulting in the experimentally observed *para*, *meta* selectivity. A detailed study of the origins of the relative stabilities of cyclohexadienyl radicals is underway and will be reported in due course.

Table 2. Comparison of Dihedral Angles (a−b−c−d) in *ortho*, *meta* TSs and *ortho*, *meta* Cyclized Radical Cations



		dihedral angle (deg)	
entry	R^3, R^4	TS	cyclized radical cation
1	R^3 = R^4 = OMe	95, **TS3***	128, **26***
2	R^3 = OMe, R^4 = Me	95, **TS5***	119, **29 ***
3	R^3, R^4 = $-OCH_2O-$	98, **TS7***	131, **32***

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Supporting Information Available: Complete ref 5 and Cartesian coordinates and energies of all reported structures and model systems. This material is available free of charge via the Internet at http://pubs.acs.org.

JA9063074

(12) The preferred planar methoxy conformation holds true for anisole. For example, see: Emsley, J. W.; Foord, E. K.; Lindon, J. C. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1211.

(13) (a) Sakurai, S.; Meinander, N.; Morris, K.; Laane, J. *J. Am. Chem. Soc.* **1999**, *121*, 5056. (b) Moon, S.; Kwon, Y.; Lee, J.; Choo, J. *J. Phys. Chem. A* **2001**, *105*, 3221.